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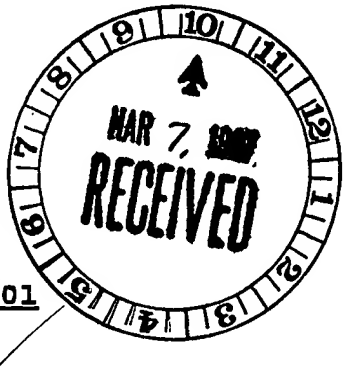

FAX COVER SHEET

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DELIVER TO: **Examiner J. Wilson**
Group Art Unit: 1211

DATE: March 7, 1997

FROM: Patrick J. Hagan, Esq.

OUR REF:

OPERATOR: Tina Doyle

YOUR REF:

Total Pages (including this cover) 18

Re: U.S. Patent Application No. 08/338,567
Filed: January 12, 1995
For: HEALTH SUPPLEMENTS CONTAINING PHYTO-OESTROGENS ANALOGUES OR METABOLITES THEREOF
By: Graham Edmund Kelly

Retransmission of February 28, 1997 fax.

Enclosures: (1) Amendment Fee Computation Sheet with Petition for Extension of Time and Certificate of Facsimile Transmission;
(2) Amendment and Request for Reconsideration Under 37 C.F.R. §1.111; and
(3) Declaration of Graham Edmund Kelly.

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of

GRAHAM EDMUND KELLY

Application No. 08/338,567

Filed: January 12, 1995

For: HEALTH SUPPLEMENTS CONTAINING PHYTO-OESTROGENS ANALOGUES OR METABOLITES THEREOF

Examiner: J. Wilson

Group Art Unit 1211

Petition for Extension Under 37 CFR §1.136(a)

The undersigned hereby petitions for an extension of time of THREE month beyond the time period set in the last office communication. The proper fee of $465.00 should be charged to the Deposit Account of the undersigned, Deposit Account No. 04-1406.

Patrick J. Hagan

PATRICK J. HAGAN

Certificate of Facsimile Transmission

I hereby certify that this paper for U.S. Patent Application No. 08/338,567 is being facsimile transmitted to the Patent and Trademark Office fax number 703-305-5246 on the date shown below.

February 28, 1997
Date of Certificate

Patrick J. Hagan

PATRICK J. HAGAN
Attorney for Applicant(s)
PTO Registration No. 27,643

Computation of Additional Fee for Amendment

[ ] No Additional Fee is required.
[X] The fee of $465.00 is authorized to be charged to the Deposit Account of the undersigned attorneys, Deposit Account No. 04-1406.

The fee has been calculated as shown below:

CLAIMS AS AMENDED				*SMALL ENTITY		OTHER THAN A SMALL ENTITY	
FOR	CLAIMS AFTER AMDT.	CLAIMS PAID FOR	NUMBER EXTRA	RATE	FEE	RATE	FEE
EFFECTIVE TOTAL CLAIMS	25	-28	= 0	$ 11	0	$ 22	
IND. CLAIMS	3	-3	= 0	39	0	78	
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIMS?				125	0	250	
PETITION FEE FOR EXTENSION 3 MONTHS					465		
				TOTAL	465	TOTAL	

*Applicant is a Small Entity, as established by a verified statement filed 1/12/95. In the event the fee calculation is in error, the Commissioner is authorized to charge any underpayment or credit any overpayment to the account of the undersigned attorneys, Account No. 04-1406. A duplicate copy of this sheet is enclosed.

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A Professional Corporation

By Patrick J. Hagan
PATRICK J. HAGAN
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of	Examiner: J. Wilson
GRAHAM EDMUND KELLY	Group Art Unit: 1211
Application No. 08/338,567	
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AMENDMENT AND REQUEST FOR RECONSIDERATION UNDER 37 C.F.R. §1.111

In response to the September 10, 1996 Official Action, please amend the above-identified application as follows:

In the Specification:

Add the attached "Abstract of the Disclosure" as the next succeeding page of the application following the claims.

In the Claims:

Claims 2, 3, 6, 7 and 9, line 1 of each claim, change "supplement" to -- composition --; and change "1" to -- 29 --.

Claims 5, 8, 21 and 22, line 1 of each claim, change "supplement" to -- composition --.

Claims 12, 14, 15, 16 and 17, line 1 of each claim, change "10" to -- 30 --.

Please add the following new claims:

29. A health supplement composition comprising an extract from soya or clover, said composition comprising any two or more phyto-estrogens of the group Genistein, Daidzein, Biochanin A, Formonoetin or the natural glycosides of any of said phyto-estrogens.

30. A method for treating or reducing the predisposition to a condition selected from the group consisting of benign breast disease, premenstrual syndrome (PMS), symptoms associated with menopause, cancer of the prostate, or elevated blood cholesterol, said method comprising administering to a subject having said condition or predisposed to said condition a therapeutically effective amount of a health supplement composition comprising an extract from soya or clover, said composition comprising any two or more phyto-estrogens of the group Genistein, Daidzein, Biochanin A, Formonoetin or the natural glycosides of any of said phyto-estrogens.

31. A method according to claim 30, wherein said composition is administered for treating or reducing the predisposition to elevated levels of cholesterol in the blood stream.

32. A method according to claim 30, wherein said composition is administered for treating cancer of the prostate.

33. A method according to claim 30, wherein said composition is administered for treating pre-menstrual syndrome (PMS).

34. A method according to claim 30, wherein said composition is administered for treating symptoms associated with menopause.

35. A method according to claim 30, wherein said composition is administered for treating benign breast disease.

36. A pharmaceutical preparation, in solid dosage unit form, consisting essentially of any two or more

concentrated, phytoestrogen-derived isoflavones selected from the group consisting of Genistein, Daidzein, Biochanin A, Formonoetin or the natural glycosides of any of said phytoestrogens.

37. A pharmaceutical preparation, as claimed in claim 36, wherein said solid dosage unit is selected from the group consisting of a pill, tablet, coated tablet, capsule or powder.

38. A pharmaceutical preparation, as claimed in claim 37, wherein said isoflavone is present in said solid dosage unit in an amount from about 20 mg. to about 200 mg. per dosage unit.

Cancel claims 1, 4, 10, 11, 18-20 and 23-28.

REMARKS

The September 10, 1996 Official Action and the references cited therein have been carefully considered. In view of the amendments presented herewith and the following remarks, favorable reconsideration and allowance of this application are respectfully requested.

In the September 10 Official Action, a formal objection has been raised under 37 C.F.R. §1.72(b), and an abstract on a separate sheet is required.

Also in the September 10 Official Action, the specification has been objected to, and claims 1-28 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to adequately teach how to make and use the claimed invention. The reasons on which these related grounds of objection and rejection are premised appear at pages 2-10 of the Official Action. These reasons include a lengthy discussion of the so-called "Forman factors" in support of the contention that undue experimentation would be required on the part of those skilled in the art in order to practice the

claimed invention. According to the Examiner, the amount of experimentation needed to verify the efficacy of the potential compositions for inclusion in a health supplement would be voluminous and unduly burdensome in view of the teachings of the instant disclosure.

Claims 1-9, 21 and 22 also stand rejected under 35 U.S.C. §103 as allegedly unpatentable in view of the disclosure of U.S. Patent 4,366,082 to Zilliken. According to the Examiner, it would have been obvious to one of ordinary skill in the art at the time the invention was made to include one or more phyto-oestrogen compounds into a composition to improve the health of the recipient, because the prior art discloses the inclusion of this class of compounds generically into compositions to be used as anti-oxidants.

Applicant, through his undersigned attorney, requested a personal interview with Examiner Wilson, which was held on February 19, 1997. The courtesy extended to applicant and his representatives in granting the interview is appreciated. The purpose of the interview was primarily to present an overview of the invention, as well as evidence as set forth in the Declaration of Dr. Kelly submitted herewith, which applicant believes clearly refutes the premise on which the §112, first paragraph, rejection is based. Certain amendatory language was discussed in connection with the broad composition and method claims, which the Examiner recommended that the applicant consider as a way of overcoming the §112, first paragraph, rejection of record.

At the conclusion of the interview, it was indicated that appropriate claim amendments would be presented to satisfy the requirements of 35 U.S.C. §112, first paragraph. The substance of the interview is fairly set forth in the Examiner Interview Summary Record (PTOL-413) in the official application file.

In accordance with the present amendment, the specification has been amended to include an abstract on a single sheet as required under 37 C.F.R. §1.72(b).

Turning to the present claim amendments, claim 1 has been rewritten as claim 29, which is directed to a health supplement composition comprising an extract from soya or clover, the composition comprising any two or more phyto-oestrogens selected from the group consisting of Genistein, Daidzein, Biochanin A, Formononetin or the natural glycosides of any of said phyto-oestrogens. Claim 10 has also been rewritten as new claim 30, which is drawn to a method for treating or reducing the predisposition to a condition selected from the group consisting of benign breast disease, premenstrual syndrome (PMS), symptoms associated with menopause, cancer of the prostate, or elevated blood cholesterol, said method comprising administering to a subject having said condition or predisposed to said condition a therapeutically effective amount of a health supplement composition comprising an extract from soya or clover, said composition comprising any two or more phyto-estrogens of the group Genistein, Daidzein, Biochanin A, Formonoetin or the natural glycosides of any of said phyto-estrogens.

New claims 31-35 are directed to the treatment and/or prevention of the following specific conditions: (i) elevated levels of cholesterol in the blood stream; (ii) cancer of the prostate; (iii) pre-menstrual syndrome; (iv) symptoms associated with menopause; and (v) benign breast disease. New claims 36-38 are directed to a particularly preferred embodiment of the invention which was discussed at the February 19, 1997 interview. Support for new claims 36-38 is provided in the present specification at page 13, line 26 through page 14, line 7 and page 16, lines 7-12.

The language of new claim 30 varies somewhat from the language discussed at the February 19 interview, because on further review it was found that the specification does not have verbatim support for the recitation "clinically predisposed". As set forth in new claim 30, the recitation "or prevention" has been deleted, as discussed at the interview, and replaced with "reducing the predisposition to"

(see page 7, line 15 of the present specification), and the recitation "at risk" has been changed to read "predisposed to said condition", which is believed to been in keeping with the substance of what was discussed at the interview. This departure from the claim language discussed at the interview was undertaken for the sake of conformity between new claim 30 and the description of the invention provided in the specification.

The present amendments further define the composition of the invention, as well as conditions described in the specification that are treatable with the composition of the invention. Support for the compositions containing extracts of soya or clover is specifically provided, for example, at pages 11 and 12 and in Examples 1 and 2 at pages 17 through 19.

The recitation of "improving the health of a human" has been omitted from the amended claims presented herewith.

No new matter has been introduced into this application by reason of these amendments.

In view of the foregoing amendments, the objection to the specification and related rejection of claims 1-28 under 35 U.S.C. §112, first paragraph, based on alleged inadequate enablement, and the 35 U.S.C. §103 rejection of claims 1-9, 21 and 22 based on the Zilliken patent are respectfully traversed.

1. As Presently Amended, Applicant's Claims Fully Comply with the Enablement Requirement of 35 U.S.C. §112, First Paragraph

Initially, it is noted that at page 3 of the September 10, 1996 Official Action, the Examiner acknowledges the sufficiency of applicant's disclosure with regard to lowering of cholesterol levels. That being the case, the objection/rejection under §112, first paragraph, is clearly inapplicable to new claim 31.

Addressing the "how to make" requirement of 35 U.S.C. §112, first paragraph, methodology for obtaining the active agents of the present invention, namely, Genistein,

Daidzein, Biochanin A, Formononetin or the natural glycosides of such phyto-oestrogens is described in detail at pages 11-13 of the present specification and exemplified in Example 1 (derivation from red clover) and Example 2 (derivation from soy beans), at pages 17-19 of the present specification. These examples produce compositions from clover and soy which are not limited only to Genistein and Daidzein, or to any specific ratio of the active agents.

Turning to the "how to use" requirement of §112, first paragraph, the pharmaceutically effective amounts of the composition are described in detail at page 14 of the specification and specifically exemplified in Examples 3 and 4. Example 3 describes the beneficial therapeutic effect of administering red clover extract to humans which is manifested in a lowering of total serum cholesterol levels, without producing any undesirable side effects. Example 4 describes the beneficial therapeutic effect of administering soy hypocotyls which is manifested in both lower cholesterol levels and amelioration of benign breast disease. Furthermore, these examples show therapeutic treatment wherein the composition of the invention is administered in an amount of 100 mg. (Example 3) and 50 mg. (Example 4) on a daily basis.

As for the additional conditions specified in the newly added claims, there is submitted herewith a Declaration of Graham Edmund Kelly, the inventor herein, which establishes that treatments conducted at his request or under his supervision, in accordance with this invention, were shown to be effective with respect to (i) prostate cancer; (ii) benign or cystic breast disease; (iii) pre-menstrual tension; and (iv) symptoms of menopause.

The Declaration of Dr. Kelly further shows that therapeutic effectiveness is evidenced when the compositions of the invention are administered in varying amounts from 40 mg to 240 mg of phyto-oestrogen, most of which are within the range described at page 14 of the present specification as the

preferred dosage amounts, and all of which are within the range disclosed as operable.

The Declaration of Dr. Kelly submitted herewith is an unsigned copy of the same Declaration that was reviewed at the February 19 interview. A signed copy of Dr. Kelly's Declaration will be submitted in a supplemental response to the September 10, 1996 Official Action.

The Declaration of Dr. Kelly provides clear evidence demonstrating that the scope of enablement provided by the present specification is fully commensurate with the scope of patent protection sought by the amended claims. Such declaration evidence is properly presented in rebutting an allegation of inadequate enablement under 35 U.S.C. §112, first paragraph. *In re Armbruster*, 185 U.S.P.Q. 152 (CCPA 1975). As was the case in *Armbruster*, the Declaration of Dr. Kelly is being submitted only to demonstrate that the teaching in the specification is adequately enabling.

In summary, the pharmaceutically effective amounts of the compositions are described specifically at page 14 of the present specification and more particularly exemplified in Examples 3 and 4. Moreover, the therapeutic treatment set forth in Dr. Kelly's declaration fully support the dosage ranges referred to at page 14. The present specification provides an enabling description of the lowering of cholesterol levels and the treatment of benign breast disease in Examples 3 and 4. The Declaration of Dr. Kelly specifically demonstrates the treatment of the additional conditions which are specifically claimed in the amendments presented herewith, namely, the treatment of prostate cancer, benign or cystic breast disease, premenstrual syndrome and symptoms associated with menopause.

For all of the foregoing reasons, the objection to the specification and related rejection of claims 1-28 under 35 U.S.C. §112, first paragraph, is untenable and should be withdrawn.

2. **The Disclosure of Zilliken Does Not Render Obvious the Subject Matter of Claims 1-9, 21 and 22**

As noted by the Board of Appeals in *Ex Parte Wolters*, 214 U.S.P.Q. 735 (Bd. Apps. 1979), the burden of establishing a *prima facie* case of obviousness falls upon the Examiner. In determining whether a case of *prima facie* obviousness exists, it is necessary to ascertain whether or not the disclosure of the cited prior art would appear to be sufficient to one of ordinary skill in the art to make the substitution, combination or other modification required to arrive at the claimed subject matter. *In re Lalu*, 223 U.S.P.Q. 1257 (Fed. Cir. 1984). In the present case, there is nothing to suggest the modification of the compounds disclosed in the Zilliken patent which is required to arrive at the composition claimed by applicant herein.

The Zilliken patent purports to disclose a class of isoflavone derivatives recoverable from a substance known as "temph", which possess anti-oxidant properties. The utility disclosed for these isoflavone derivatives is in the "stabilization of a wide variety of food products including edible fats and oils" (see column 2, lines 20-22).

All of the isoflavone derivatives disclosed in the Zilliken patent as possessing anti-oxidant properties have an -OR substituent in the 6-position of the structural formula, wherein R may be a methyl, ethyl or hydrogen substituent, as described at columns 2 and 3 of the Zilliken patent. The active agent incorporated in the compositions of the present invention, by contrast, are unsubstituted in the 6-position. See the structural formula set out at page 9 of the present specification.

Although the Zilliken patent acknowledges that Genistein and Daidzein are recoverable from temph, there is no clear disclosure that Genistein and Daidzein possess anti-oxidant properties, or indeed are within the ambit of the invention described and claimed in the Zilliken patent. On

the contrary, a review of the Zilliken patent claims plainly reveals that Genistein and Daidzein are outside the scope of the claimed invention for the reasons stated above, i.e., all of the isoflavone derivatives identified as having the desired anti-oxidant properties include a substituent in the 6-position of the claimed structural formula.

Thus, the evidence of alleged obviousness in this case fails to show or suggest the removal of the -OR substituent from the isoflavone derivatives disclosed in the Zilliken patent, which is required to arrive at the compounds included in the compositions of the present invention. In the absence of such showing or suggestion, there is inadequate support for the Examiner's position that the compositions claimed by applicant herein would have been *prima facie* obvious. *Cf., In re Grabiak*, 226 U.S.P.Q. 870 (Fed. Cir. 1985).

Furthermore, the molecular modification of the Zilliken isoflavone derivatives which is required to arrive at the active agents of the present invention cannot be presumed to be obvious from the disclosure of the Zilliken patent, inasmuch as such modification would be clearly contrary to the invention which is the subject of the Zilliken patent, i.e., isoflavone derivatives having an -OR substituent at the 6-position of the structural formula. *Cf., Ex Parte Hartman*, 186 U.S.P.Q. 366 (Bd. Apps. 1974).

Furthermore, the Zilliken patent plainly fails to show or suggest the ratios, dosage amounts and dosage forms called for in applicant's claims 6-9, as well as the pharmaceutical preparation of new claims 36-38.

Inasmuch as the Zilliken patent fails to show or suggest the claimed subject matter as a whole, it necessarily follows that the Zilliken patent does not render applicant's claims 1-9, 21 and 22 *prima facie* obvious. Therefore, no evidence of unusual or unexpected results needs to be presented in this case. *In re Lunsford*, 148 U.S.P.Q. 721 (CCPA 1966).

In summary, the rejection of claims 1-9, 21 and 22 under 35 U.S.C. §103 based on the disclosure of the Zilliken patent is improper and should be withdrawn.

In view of the amendments presented herewith, the Declaration of Dr. Kelly and the foregoing remarks, it is respectfully urged that the objections and rejections set forth in the September 10, 1996 Official Action be withdrawn and that this application be passed to issue, and such action is earnestly solicited.

Respectfully submitted,

DANN, DORFMAN, HERRELL AND SKILLMAN
A Professional Corporation

By Patrick J. Hagan
PATRICK J. HAGAN
PTO Registration No. 27,643

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Enclosure: Declaration of Graham Edmund Kelly

ABSTRACT OF THE DISCLOSURE

Compositions enriched with natural phyto-oestrogens or analogues thereof selected from Genistein, Daidzein, Formononetin and Biochanin A. These may be used as food additives, tablets or capsules for treatment or prevention of certain cancers, pre-menstrual syndrome, menopause or hypercholesterolemia.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of	Examiner: J. Wilson
GRAHAM EDMUND KELLY	Group Art Unit: 1211
Application No. 08/338,567	
Filed: January 12, 1995	
For: HEALTH SUPPLEMENTS CONTAINING PHYTO-OESTROGENS ANALOGUES OR METABOLITES THEREOF	

DECLARATION OF GRAHAM EDMUND KELLY UNDER 37 C.F.R. §1.132

I, Graham Edmund Kelly, a citizen of the Commonwealth of Australia, residing at 1/47 Coolawin Road, Northbridge, New South Wales, Commonwealth of Australia, do solemnly and sincerely declare as follows:

1. I am Chief Executive Officer of Norvet Ltd. and am the inventor of the subject application.

2. I am a research scientist and hold the degrees of Bachelor of Science (Vet) from the University of Sydney (1968); Bachelor of Veterinary Science from the University of Sydney (1969); and Doctor of Philosophy from the University of Sydney (1972). I have worked in the field of medical and veterinary research for approximately twenty-five years.

3. I have read the Office Action in connection with U.S. Patent Application No. 08/338,567 by Examiner Wilson, dated 10 September 1996.

4. The health supplement composition comprising an extract from soya or clover as claimed in the patent application has been used in a series of therapeutic treatments conducted at my request and/or under my supervision. Details of these treatments are set forth below.

Compositions

Compositions comprising an extract of soya or clover were prepared in accordance with Examples 1 and 2 at pages 18 and 19 of the subject application 08/338,567. These compositions, for convenience referred to as "the inventive composition", were prepared comprising 40 mg, 80 mg, 120 mg, 160 mg and 240 mg of phyto-estrogen.

Treatments

Prostate Cancer

Two patients diagnosed with prostate cancer were treated initially with the inventive composition comprising 240 mg per day, and subsequently 120 mg per day phyto-estrogen. The PSA levels, a marker for prostate cancer, were stabilized in these patients and there has been no rise in the PSA levels subsequently. This demonstrates the treatment of prostatic cancer in these individuals.

A further patient diagnosed with malignant prostate cancer (PSA 13.1 μg/L) was treated with the inventive composition. The patient was treated with the composition comprising 160 mg per day phyto-estrogen, seven days prior to prostatectomy. Histological comparison was made of the pre-operative needle biopsy and the prostatectomy specimen. The needle biopsy revealed low grade infiltrating adenocarcinoma. The prostatectomy specimen showed mild patchy microvacuolation and prominent apoptosis (programmed cell death). Lymph nodes were negative for malignancy. The degenerative changes in the prostatectomy specimen, especially the apoptosis, show treatment of the prostatic cancer.

Benign or Cystic Breast Disease

A patient with benign or cystic breast disease was treated with 160 mg of the inventive composition administered orally on a daily basis. The patient exhibited no breast tenderness, which was maintained when the dosage level was reduced to 80 mg. Her symptoms did not return and she continues to have relief from mastalgia.

Pre-Menstrual Syndrome (PMS)

Nine women were treated with 80 mg per day of the inventive composition and were screened for the well-described symptoms of PMS including psychological, psychiatric, gynecological and personal status. Relief from PMS in these various symptoms was observed across the treatment group.

Menopause

Eight menopausal women were divided into two groups of four and treated with either 40 mg or 160 mg of the inventive composition administered orally on a daily basis. Four patients were also treated with a placebo composition. Indicators measured were incidence or severity of hot flushes, night sweats. Green score, vaginal pH, vaginal cytology and mean cholesterol levels across the treatment groups. A significant change in menstrual symptoms was observed and a dose response change was observed between the 40 mg and 160 mg dosage range. This indicating that 160 mg per day was the most effective dosage for treatment of menopausal symptoms.

5. These studies show that a composition according to the invention described and claimed in U.S. Patent Application No. 08/338,567 is effective in the treatment of:

- Prostate cancer

- Benign or cystic breast disease (mastalgia)
- Pre-menstrual syndrome
- Symptoms of menopause

6. As shown in the Examples 3 and 4 at pages 19 and 20 of the subject application 08/338,567, a composition according to the invention was effective in the treatment of elevated levels of cholesterol in the blood stream.

The undersigned declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further, that the statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and such willful false statements may jeopardize the validity of the application or patent issuing thereon.

DATE

GRAHAM EDMUND KELLY